

Answer 1:

Bibliographic Information

Pemetrexed improves tumor selectivity of ^{111}In -DTPA-folate in mice with folate receptor-positive ovarian cancer. Mueller, Cristina; Schibli, Roger; Krenning, Eric P.; de Jong, Marion. Department of Nuclear Medicine, Erasmus Medical Center, Rotterdam, Neth. *Journal of Nuclear Medicine* (2008), 49(4), 623-629. Publisher: Society of Nuclear Medicine, CODEN: JNMEAQ ISSN: 0161-5505. Journal written in English. AN 2008:539369 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Folate-based radiopharmaceuticals can be used as imaging agents and for potential radiotherapy of folate receptor (FR)-pos. malignant tissue (e.g., ovarian carcinomas). However, substantial FR expression in the kidneys results in undesired renal retention of radioactivity. Recently, we found that the preinjection of an antifolate significantly improved tumor selectivity of organometallic ^{99m}Tc -radiofolates in mice. The aim of this study was to corroborate the effect of pemetrexed with the clin. tested ^{111}In -DTPA-folate (DTPA is diethylenetriaminepentaacetic acid) in a human ovarian cancer xenografted mouse model. Methods: In vivo studies were performed in female athymic nude mice bearing s.c. FR-pos. ovarian tumors (IGROV-1 and SKOV-3) or metastases (after i.p. SKOV-3 cell inoculation). Biodistribution studies were performed 1, 4, and 24 h after administration of ^{111}In -DTPA-folate (0.7 MBq/mouse, 0.35 μg) with or without preinjection of pemetrexed (PMX, 400 μg) 1 h before the radiofolate. Images were acquired with a high-resoln., high-sensitivity SPECT/CT camera, 4 and 24 h after injection of the radiotracer (30-50 MBq/mouse, 4.5-10 μg). Results: In biodistribution studies the tumor uptake of ^{111}In -DTPA-folate (IGROV-1: 9.79 ± 3.21 %ID/g [percentage injected dose per g]; SKOV-3: 7.57 ± 0.61 %ID/g, 4 h after injection) was high and retained over the time of investigation. However, considerable retention of radioactivity was found in kidneys (85-105 %ID/g, 4 h after injection), resulting in unfavorably low tumor-to-kidney ratios (.apprx.0.10). Preinjection of PMX resulted in a significant redn. of renal uptake (20%-30% of control values, $P < 0.03$) at all time points after injection of ^{111}In -DTPA-folate, whereas the tumor uptake was retained. Thus, the tumor-to-kidney ratio was significantly increased to .apprx.0.50. SPECT/CT images confirmed the superior tumor-to-background ratio in mice injected with PMX.

These findings were particularly evident in mice with SKOV-3 metastases that could be visualized only when ^{111}In -DTPA-folate was administered in combination with PMX. Conclusion: The application of PMX resulted in a significant redn. of undesired radioactivity accumulation in kidneys, whereas the tumor uptake remained unaffected. These observations suggest a general validity of the reducing effect of PMX on the uptake of radiofolates in kidneys. Our findings will lead the way toward the development of folate-based radiotherapy.

Answer 2:

Bibliographic Information

Imatinib Mesylate Enhances Therapeutic Effects of Gemcitabine in Human Malignant Mesothelioma Xenografts. Bertino, Pietro; Piccardi, Federica; Porta, Camillo; Favoni, Roberto; Cilli, Michele; Mutti, Luciano; Gaudino, Giovanni. Department of Chemical, Food, Pharmaceutical and Pharmacological Sciences and Drug and Food Biotechnology Center, University of Piemonte Orientale A. Avogadro, Novara, Italy. *Clinical Cancer Research* (2008), 14(2), 541-548. Publisher: American Association for Cancer Research, CODEN: CCRE4 ISSN: 1078-0432. Journal written in English. CAN 149:118850 AN 2008:106226 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: Platelet-derived growth factor receptor β (PDGFR β), frequently activated in malignant mesothelioma, is a promising cancer therapeutic target. Imatinib mesylate (STI571; Glivec) is a selective inhibitor of tyrosine kinases as bcr-abl, c-kit, c-fms, and PDGFR β and enhances tumor drug uptake by reducing the interstitial fluid pressure. We previously showed that imatinib mesylate synergizes with gemcitabine and pemetrexed in PDGFR β -pos. mesothelioma cells. Here, we aimed at investigating these combined treatments in a novel mesothelioma model. **Exptl. Design:** REN mesothelioma cells, infected with a lentiviral vector carrying the luciferase gene, were injected in the peritoneum of severe combined immunodeficient mice. This model allowed imaging of live animals treated with pemetrexed or gemcitabine chemotherapeutics, or with imatinib mesylate alone, as well as with a combination of gemcitabine and

imatinib mesylate. RESULTS: We show here that, consistent with our previous in vitro studies, gemcitabine inhibited tumor growth, whereas pemetrexed was ineffective, even at the highest dosage tested. Compared with monotreatment, the combination of gemcitabine with imatinib mesylate led to a further tumor growth inhibition and improved mice survival, by a decrease rate of tumor cell proliferation and an increase in no. of apoptotic tumor cells. CONCLUSIONS: Imatinib mesylate enhances the therapeutic response to gemcitabine, in accordance with our previous in vitro data. These in vivo results validate imatinib mesylate and gemcitabine as a combination treatment of malignant mesothelioma, also in view of its known pos. effects on tumor drug uptake. These evidences provide the rationale for the currently ongoing clin. trials.